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CONTEMPORARY REVIEW

Change of Heart: The Underexplored Role of Plaque Hemorrhage in the Evaluation of Stroke of Undetermined Etiology

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ABSTRACT: In the evaluation of embolic strokes of undetermined source, great emphasis is often placed on cardiovascular disease, namely on atrial fibrillation. Other pathophysiologic mechanisms, however, may also be involved. Carotid artery intraplaque hemorrhage (IPH)—the presence of blood components within an atheromatous plaque—has become increasingly recognized as a possible etiologic mechanism in some cryptogenic strokes. IPH is a marker of plaque instability and is associated with ipsilateral neurologic ischemic events, even in nonstenotic carotid plaques. As recognition of carotid IPH as an etiology of embolic strokes has grown, so too has the complexity with which such patients are evaluated and treated, particularly because overlaps exist in the risk factors for atrial fibrillation and IPH. In this article, we review what is currently known about carotid IPH and how this clinical entity should be approached in the context of the evaluation of embolic strokes of undetermined source.

Key Words: atrial fibrillation ■ cardiovascular diseases ■ carotid arteries ■ embolic stroke ■ plaque, atherosclerotic

Establishing the etiology of embolic strokes is of central importance in designing and implementing preventive and therapeutic strategies. In the current era, there has been great emphasis on the importance of atrial fibrillation (AF) in the field because of both its frequency and its association with a 5-fold increase in stroke risk.[1,2] However, not all embolic strokes are explained by AF. Indeed, the etiology of stroke remains unknown in 25% to 40% of embolic strokes.[3,4] These strokes are classified as embolic strokes of undetermined source (ESUS). To further understand the mechanism of ESUS, prolonged monitoring for AF and screening for patent foramen ovale and aortic and carotid disease have been suggested. Yet, embolic strokes continue to occur even in the absence of all these potential competing risks, leading to an ongoing clinical conundrum. Attention has recently been turned to other pathophysiologic mechanisms such as intracranial vessel wall inflammation and unstable intracranial atherosclerosis. Increasingly, however, carotid intraplaque hemorrhage (IPH) has been established as a major cause of recurrent strokes.[5–8]

WHAT IS IPH?

IPH fundamentally describes hematogenous constituents liberated from extravasation of blood cells within atheromatous plaque. Multiple factors of IPH development have been described, including the disruption of the fibrous cap[9] and the process of neovascularization, which develops from adventitial vasa vasora and grows centrally into the plaque.[10–13] These vessels, felt to be the result of chronic excess secretion of vascular endothelial growth factor, are disorganized, lack smooth muscle cells, and have endothelial gap junctions—all of which are features that make them susceptible to leaking. Furthermore, a variety of cells including erythrocytes, platelets, leucocytes, neutrophils, and macrophages are recruited

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Nonstandard Abbreviations and Acronyms

CEA	carotid endarterectomy
ESUS	embolic strokes of unknown source
IPH	intraplaque hemorrhage
LRNC	lipid-rich necrotic core

during the process of neovascularization, resulting in vulnerability of the plaque and potentiating thrombus formation.[5,6,11] These processes form the pathophysiology of an unstable plaque that can result in shedding of thrombus into the circulation or embolization of clot and plaque elements. The development of unstable atherosclerotic features can also lead to plaque growth, as recurrent episodes of instability are followed by healing, resulting in the formation of plaque layers, and progressively worsening stenosis.[14] Similar layering has also been described as part of the process of developing extensive coronary artery disease.[12,15]

IDENTIFICATION OF IPH

Multiple imaging modalities have been studied for the role in identification of plaque hemorrhage. Unfortunately, computed tomography (CT) and ultrasound, though more ubiquitous in clinical practice, are generally unable to differentiate IPH from lipid-rich necrotic core (LRNC). On CT, IPH and LRNC both appear as relatively low-density regions and are generally combined under the descriptor of "soft plaque" components. Attempts to differentiate IPH from LRNC based on CT attenuation values have produced contradictory results.[16,17] Accordingly, tissue characteristics of IPH in these modalities overlaps with LRNC, which limits their specificity. Sonography, similarly, is able to characterize the degree of luminal stenosis and can detect vascular calcifications but cannot differentiate between IPH and LRNC.[18] Currently, neither CT nor ultrasound is routinely used in clinical practice to identify carotid IPH.

As such, magnetic resonance imaging (MRI) with vessel wall imaging has emerged as the most sensitive and specific noninvasive imaging modality for IPH identification.[10,19–24] The ideal imaging sequences for identification of IPH on MRI are black blood (ie, flowing blood is dark) T1 weighted images (Figures 1 and 2). Many institutions, including our own, rely heavily on 3-dimensional T1 weighted gradient-echo images (MPRAGE), where IPH appears as a hyperintense plaque component that is identified as a hyperintense plaque with a signal intensity 50% higher than the adjacent sternocleidomastoid muscle. Other MRI sequences for identifying IPH do exist. Recently, a simultaneous noncontrast angiography and IPH sequence has been introduced that can detect IPH, which has strong (k=0.82) agreement with MPRAGE.[25] The increased recognition of IPH as a contributor to ipsilateral neurologic symptoms has made the use of MPRAGE images more common. At our institution, MPRAGE images are now routinely obtained during each neck MR angiography examination, which provides substantial clinical information at a relatively little time expenditure (3 minutes 15 seconds). Because of its negligible time cost, we recommend all institutions to similarly incorporate this into their routine MR angiography protocols.

Of note, multiple other high-risk plaque features can also be identified on MR angiography. The most well

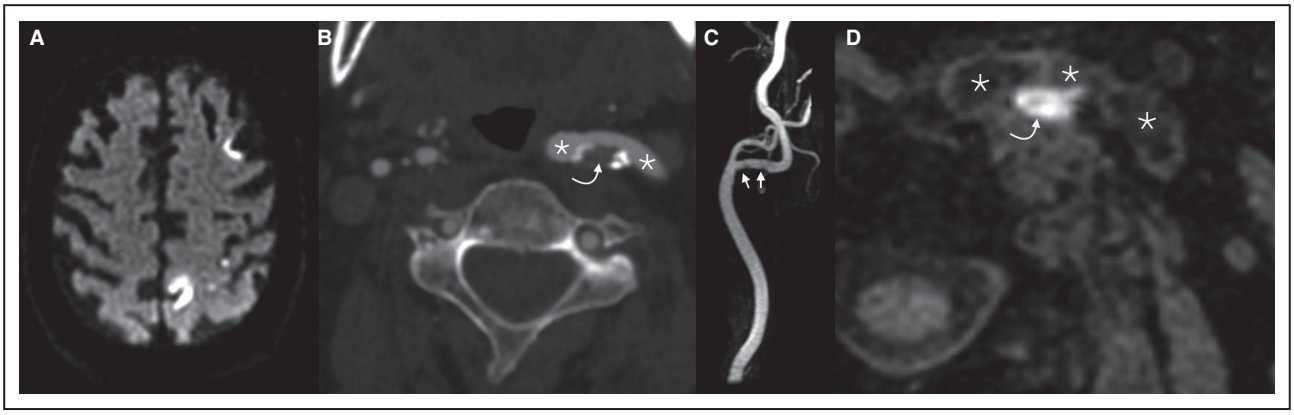

Figure 1. Example of intraplaque hemorrhage (IPH).
Axial DWI of the brain (**A**) demonstrates acute infarcts of the left cerebral hemisphere. A neck CTA (**B**) showed a predominantly low-density plaque in the proximal left ICA, with <50% stenosis of the vessel lumen (curved arrow). 3D construction MRA of the neck (**C**) confirmed the nonstenotic plaque (straight arrows). On MPRAGE images (**D**), marked hyperintensity was seen within the central plaque (curved arrow), compatible with IPH (asterisks indicate arterial lumen on **B** and **D**). CTA indicates computed tomography angiography; DWI, diffusion weighted imaging; ICA, internal carotid artery; IPH, intraplaque hemorrhage; MPRAGE, magnetization-prepared rapid acquisition gradient echo; and MRA, magnetic resonance angiography.

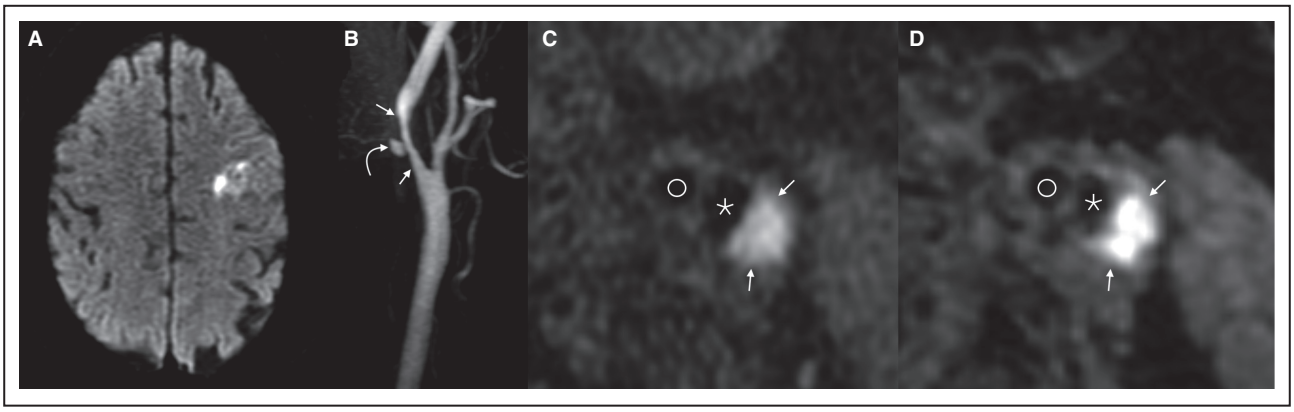

Figure 2. Example of intraplaque hemorrhage within a culprit carotid atherosclerotic lesion.
Axial DWI (**A**) demonstrated an acute left frontal lobe stroke. 3D constructed MRA imaging of the left carotid vasculature (**B**) showed a plaque within the proximal left ICA (between straight arrows). An outpouching into the plaque (curved arrow) was compatible with a large ulceration. Axial reformats of fat saturated T1 cube (**C**) images revealed a large lipid rich necrotic core within the plaque (between straight arrows, **C**). Hyperintense signal within the majority of this area on MPRAGE images (**D**) was consistent with superimposed intraplaque hemorrhage. (Circle and asterisk show external and internal carotid artery lumens, respectively.) DWI indicates diffusion weighted imaging; MPRAGE, magnetization-prepared rapid acquisition gradient echo; and MRA, magnetic resonance angiography.

recognized of these so-called "vulnerable plaque" features are LRNC, plaque ulcerations, and plaque rupture with thrombosis.[26] On MRI, LRNC is isointense (though sometimes minimally hypo- to hyperintense) to adjacent soft tissues on fat-saturated T1-weighted images. On contrast-enhanced images, thin peripheral enhancement is seen around the margins of LRNC, likely representing enhancement of the vessel wall and fibrous cap. Ulcerations appear as a focal outpouching of the lumen into the plaque; thromboses appear as a filling defect within the center of the vessel lumen, surrounded on all sides by intraluminal blood.[26]

CLINICAL SIGNIFICANCE OF IPH

The presence of IPH is in and of itself a destabilizing factor in the natural history of an atheromatous plaque. This is independent of the degree of stenosis and explains the well-described phenomenon of nonstenotic plaques resulting in thromboembolic events in multiple vascular beds. Carotid plaque hemorrhage has repeatedly been shown to be associated with acute and future ipsilateral neurologic events (Table).[27–32] Saam et al, in a meta-analysis of 689 patients who underwent MRI carotid plaque imaging, found that patients with carotid IPH had a 6-fold higher risk for ipsilateral neurologic ischemic events, with a hazard ratio of 5.89. This equated to a 17% annual risk of cerebrovascular events in patients with IPH, compared with 2.4% in patients without IPH.[33]

Another meta-analysis, by Schindler et al, found that among patients with symptomatic carotid stenosis (>70%), the risk of ipsilateral stroke was 29.3%, compared with 1.5% annual risk in those without IPH.[5]

In patients with a stenosis of 50% to 69%, the annual rate of stroke was 18.1% for patients with IPH and 2.1% for those without; for patients with <50% stenosis, the annual rate of stroke was 9.0% for those with IPH and 0.7% for those without IPH. Among asymptomatic carotid stenosis patients, the presence of IPH was associated with an annualized event rate was 5.4% compared with just 0.8% among those without IPH. Accordingly, the presence of IPH is associated with more frequent adverse outcomes irrespective of the degree of stenosis.[5]

WHY SHOULD CARDIOLOGISTS CARE?

The most significant implication for cardiologists of carotid IPH is in the workup and evaluation of stroke.[34] The cardiology community has often focused on AF or patent foramen ovale as the major mechanisms of stroke. In contrast, multiple neurological studies have shown that nonstenotic carotid plaques with IPH are seen in up to 40% of patients with ESUS.[35] In one recently published article from our institution, of 123 patients with ESUS, 25% had ipsilateral plaque hemorrhage and the stroke recurrence rate in these patients was 9%/year compared with just 2.5%/year in the non-IPH group.[36] In the CAPIAS (Carotid Plaque Imaging in Acute Stroke) trial, 31% of patients with ESUS had a complicated nonstenotic plaque ipsilateral to their stroke.[8,37–40] Multiple additional studies and meta-analyses have confirmed these results.[8,37–40]

Aside from stroke risk and stroke workup, the presence of carotid IPH has been found to be an

Table. Studies Demonstrating an Association Between Carotid Artery Intraplaque Hemorrhage and Ischemic Strokes

Authors	Year	Meta-analysis	No. of patients	Results
Mark et al[27]	2021	Yes	354	Odds ratio of IPH ipsilateral to embolic stroke of undetermined source compared with contralateral carotid: 6.9
Larson et al[28]	2021	No	123	Annual rate of recurrent stroke in patients with IPH is 9.5%, compared with 2.5% in patients without IPH
Gupta et al[29]	2013	Yes	779	Hazard ratio of IPH for ipsilateral stroke or transient ischemic attack: 4.59
Liu et al[30]	2019	No	687	Volume of IPH associated with infarct (odds ratio=2.5)
McNally et al[31]	2015	No	726	Odds ratio of ipsilateral IPH in setting of ipsilateral acute stroke: 25.2
Deng et al[32]	2020	Yes	621	Hazard ratio of IPH for recurrent stroke or transient ischemic attack: 7.1

IPH indicates intraplaque hemorrhage.

independent predictor for major cardiovascular events including myocardial infarction. For example, in a study by Singh et al, 62.5% of patients with IPH had suffered a major cardiovascular event other than stroke compared with just 20% of patients without IPH.[41] A prognostic study of 818 patients found that 31% of patients with IPH had a cardiovascular event at 3 years of follow-up compared with just 17.2% of those without IPH.[42] This is probably due to the fact that presence of carotid plaque is reflective of plaque burden in other beds and its association with cardiovascular risk factors in general.[43] Nevertheless, it should be mentioned there are multiple other markers for overall atherosclerotic plaque burden, including ankle-brachial index, degree of stenosis, and various biomarkers.

So, what is the cardiologist to do with patient with patients diagnosed with embolic strokes of undetermined source? First, the diagnosis of ESUS should be established by (1) identifying a nonlacunar ischemic infarct on imaging; (2) noting absence of arterial occlusion or significant (≥50%) stenosis in the ipsilateral arterial vasculature; (3) ruling out a cardiac source of emboli, typically through echocardiography and cardiac monitoring; and (4) excluding any other possible source (eg, drug abuse, arterial dissection, clotting disorders such as antiphospholipid syndrome) through a combination of clinical assessment, imaging evaluation, and laboratory workup. Then, once the diagnosis of ESUS is confirmed, MRI carotid plaque imaging should be considered as a next step to assess for the presence of IPH or other vulnerable plaque features.

A COMPLICATED CHANGE OF HEART

In our practice, as in many others, a common clinical scenario occurs in patients with a history of unexplained strokes or transient ischemic attacks. In such patients, monitoring for unsuspected AF is important and can be accomplished with implantable devices or extended Holter monitoring. In some settings, these unexplained events could have occurred while on an oral anticoagulant or despite receiving a left atrial appendage occlusion device, or in the absence of documented AF. In these situations, the clinical event may not have been the failure of the strategy that had been chosen—either oral anticoagulant or an occlusion device, but instead failure to recognize and treat an alternative etiology. In this setting, the application of dedicated carotid plaque MRI imaging should become more routine. Today, vessel wall imaging is increasingly used as a tool in determining stroke etiology.[44]

However, these arguments deserve a little more nuance. First, in the evaluation of ESUS, which patients should be routinely triaged to vessel wall imaging of the carotid arteries? In our practice when we examined the prevalence of IPH by decade of life, we found that plaque hemorrhage was exceptionally rare among patients under the age of 50 and that these patients were highly unlikely to benefit from plaque imaging, whereas the prevalence of IPH increased significantly with age.[45] In patients over 50, performing plaque imaging in all patients who are undergoing MRI is a viable option, though it comes at a higher financial cost and time on a MRI scanner. Routine clinical practice at most institutions in the evaluation of acute ischemic stroke is to obtain an ultrasound of the carotids or a CT angiography. Data under review from our group (still unpublished) have found that plaque hemorrhage is all but absent in patients with a carotid artery wall thickness <3 mm, so this threshold may serve as a potential means for triage of patients to carotid imaging as well. Thus, it is possible that screening for carotid IPH in young patients, or those with <3 mm wall thickness, may yield few positive cases. For now, however, these considerations are not incorporated routinely into how patients are worked up at our institution; carotid plaque imaging studies are typically performed regardless of age and sonographic findings. Incorporation of imaging in patients with stroke of undetermined source includes multiple pathways (Figure 3). In adult patients with a suspected embolic stroke, the first step is to consider its most likely source. The distribution is particularly useful: infarcts that occur in more than one arterial

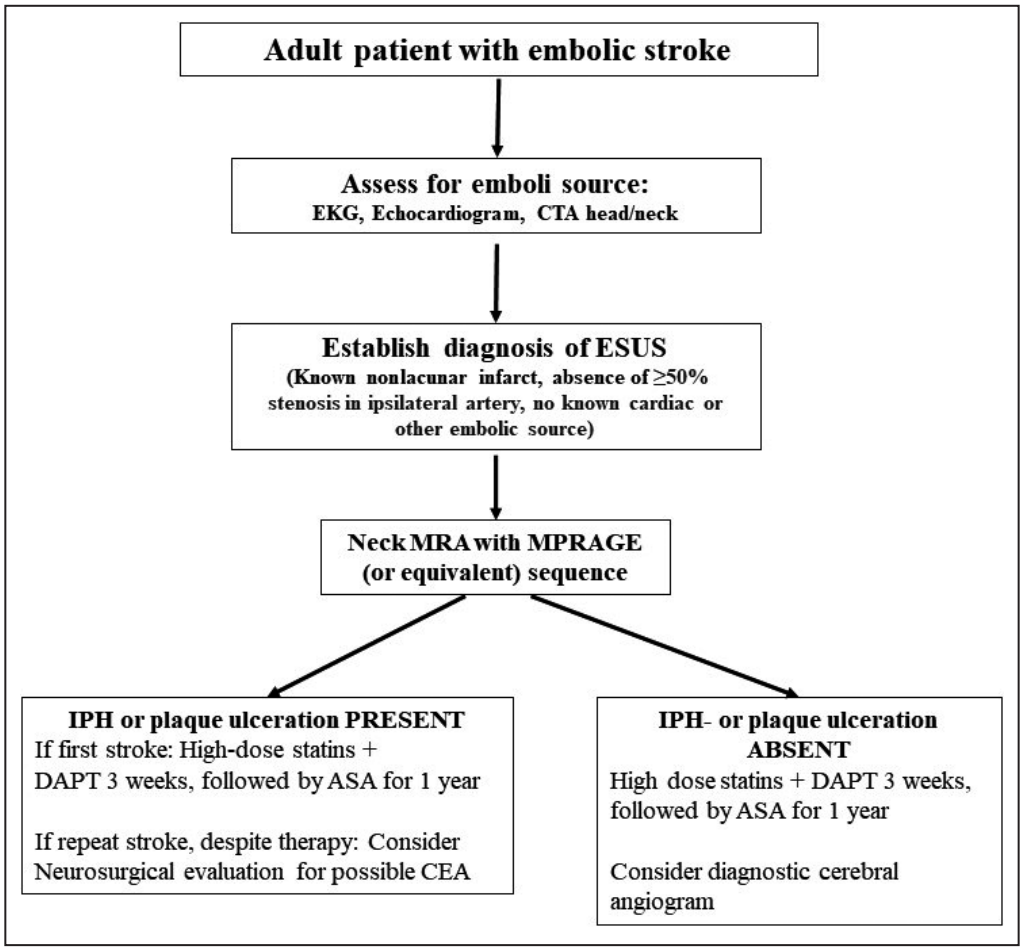

Figure 3. Embolic stroke of undetermined source workup.
This flow chart shows how our institution currently assesses, and treats, patients with embolic strokes of undetermined source. ASA indicates aspirin; CEA, carotid endarterectomy; CTA, computed tomography angiography; DAPT, dual antiplatelet therapy; ESUS, embolic stroke of undetermined source; IPH, intraplaque hemorrhage; MPRAGE, magnetization-prepared rapid acquisition gradient echo; and MRA, magnetic resonance angiography.

territory (eg, bilateral) are often embolic and from a distant (ie, noncarotid) source. Strokes localized to a single arterial territory, if embolic, are often from the ipsilateral carotid artery.

In the setting of suspected embolic strokes, a proposed algorithm for workup and treatment is proposed in Figure 4. For all patients, ECG should be performed aimed at evaluating the possibility of AF. More prolonged cardiac monitoring (30 days) should be performed if a cardiac source is strongly considered. In addition, echocardiography should be obtained to assess for the presence of structural heart disease such as patent foramen ovale. If a patent foramen ovale is identified, high-risk features such as atrial septal aneurysm should be taken into consideration.

Next, the carotid arteries should be imaged to assess for any significant stenosis. This can be done using either carotid ultrasound or CT angiography. A severe (>70%) stenosis located ipsilateral to unilateral/single vascular territory infarcts should be considered for a culprit lesion. If both arteries have <50% luminal narrowing, however, and no other cause of embolic infarct has been discovered, the strokes should be considered ESUS. In such cases, MR angiography with MPRAGE sequence imaging should be employed to assess for high-risk plaque features—particularly IPH and plaque ulceration.

If IPH is documented, then clinical consideration includes medical therapy with dual antiplatelet therapy and careful control of other risk factors including high-dose statins, blood pressure control, and cessation of tobacco. Careful clinical follow-up is recommended to assess for recurrent symptoms. If such patients have a repeat stroke despite adherence to this therapy, one should consider neurosurgical consultation for possible carotid endarterectomy (CEA).

Perhaps the most complex scenario is the patient with concurrent potential cardiac and carotid culprits

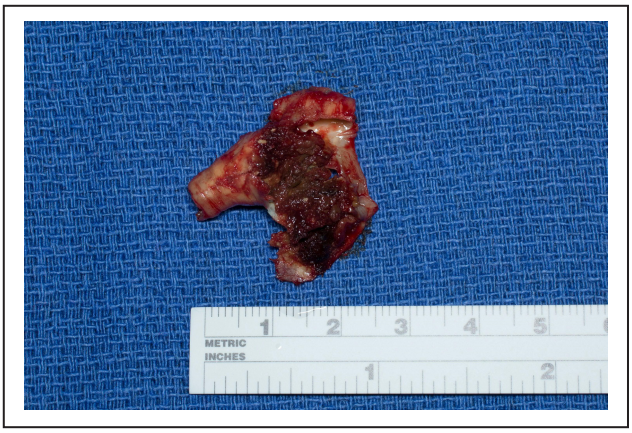

Figure 4. Operative finding.
Operative finding at the time of CEA documenting intraplaque hemorrhage. CEA indicates carotid endarterectomy.

for stroke (ie, the 75-year-old with a carotid stenosis and AF). This remains a topic for future rigorous study. We can speculate, however, that in such cases the presence of a plaque hemorrhage in the setting of unilateral ischemia could serve as a tiebreaker tilting the balance in favor of the carotid artery as the cause of the patient's stroke. The use of oral anticoagulation is uncertain as anticoagulation may be associated with the presence of IPH and may worsen plaque instability.[37]

WHAT DO WE DO ABOUT IPH?

Specific treatment directed at IPH remains poorly studied. In selected patients, particularly those with recurrent cryptogenic events after documentation of IPH, CEA, or less often carotid stenting can be considered even though the degree of carotid stenosis is not severe and by standard criteria would not merit CEA/carotid stenting[34,46] (Figure 4). Rates of recurrent strokes among such patients undergoing CEA are exceptionally low, particularly in patients with <50% stenosis, suggesting that in appropriately selected patients this may be a feasible option.[28] Still, this is not without risk: a meta-analysis by Brinjikji et al noted that the rate of postoperative strokes after carotid stenting was higher in patients with IPH, likely because such unstable plaques were more likely to seed emboli.[47] Our institution has begun treating some patients with nonstenotic carotid IPH with CEA or carotid stenting with anecdotal success. Nevertheless, this remains a contentious issue across institutions.

Medical treatment options range from dual antiplatelet therapy to oral anticoagulant, though the efficacy of these strategies may be limited. If intraluminal thrombus is already present, dual antiplatelet therapy may not be effective. The effects of statin therapy have been the focus of considerable analysis, including a recent systematic review and meta-analysis of 361 patients that reported the effect of statins on changes in carotid plaque composition.[48] In that study, the authors identified a significant decrease in lipid-rich-necrotic core volumes when assessed at >12 months of treatment but no change when imaged at shorter durations of therapy. It is possible that by decreasing these pathologic substrates, the development of IPH may be retarded. Further studies are needed to identify novel minimally invasive plaque modification techniques that may help stabilize and eventually heal IPH.

CONCLUSIONS

The pathophysiology of embolic stroke is of increased importance as different therapeutic strategies are available. Left atrial appendage occlusion in patients with nonvalvular AF at risk for stroke is increasingly used for local site-specific therapy. However, in patients with stroke IPH is an increasingly widely recognized component of risk in patients with carotid arterial disease and should be considered along with other strategies in the evaluation of patients with ESUS. Identification by MRI with carotid plaque imaging is the standard for diagnosis. Definitive treatment strategies for carotid IPH have yet to be established. Nevertheless, optimal medical therapy with antiplatelet and statin therapy is essential, as is control of risk factors such as hypertension and smoking.

ARTICLE INFORMATION

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Disclosures

None.

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